AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Bendamustine in combination with rituximab for the treatment of previously untreated and relapsed indolent lymphomas

September 2020

ONE WALES INTERIM COMMISSIONING DECISION

Bendamustine in combination with rituximab for the treatment of previously untreated and relapsed indolent lymphomas

Date of original advice: April 2017
Date of review: September 2020

The following Interim Pathways Commissioning Group (IPCG) recommendation has been endorsed by health board Chief Executives.

Bendamustine in combination with rituximab can continue to be made available within NHS Wales for the treatment of previously untreated and relapsed follicular lymphoma, marginal zone lymphoma and Waldenstrom's macroglobulinaemia under the following circumstances:

- In the first-line setting, for use in fit patients with aggressive follicular lymphoma and marginal zone lymphoma where other licensed and health technology appraisal-approved regimens are unsuitable.
- In the relapsed setting, for use in patients with follicular lymphoma and marginal zone lymphoma where other licensed and health technology appraisal-approved regimens are unsuitable.
- For the treatment of Waldenstrom's macroglobulinaemia for first-line and relapsed disease in patients deemed unsuitable for anthracycline-based regimens and/or where other licensed and health technology appraisal-approved regimens are unsuitable.

Bendamustine in combination with rituximab is not a licensed regimen to treat this indication and is therefore 'off-label'. Each provider organisation must ensure all internal governance arrangements are completed before these medicines are prescribed in combination.

The risks and benefits of the off-label use of bendamustine with rituximab for this indication should be clearly stated and discussed with the patient to allow informed consent.

Providers should consult the General Medical Council Guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

This advice will be reviewed after 12 months or earlier if new evidence becomes available.

Clinician responsibility
Clinicians will be obliged to collect and monitor patient outcomes. Evidence of clinical outcomes will be taken into consideration when reviewing the One Wales Interim Commissioning decision.

Health board responsibility
Health boards will take responsibility for implementing One Wales Interim Commissioning decisions and ensuring that a process is in place for monitoring clinical outcomes.

One Wales advice promotes consistency of access across NHS Wales.

This is a summary of new evidence available and patient outcome data collected, to inform the review.

Background
Bendamustine with rituximab is available in NHS England through clinical commissioning for the first-line treatment of advanced, indolent non-Hodgkin's lymphoma[1]. Bendamustine is available through NHS England's Cancer Drugs Fund for use in relapsed low grade lymphoma, in people for whom standard treatment is unsuitable[2]. According to the NHS England Cancer Drugs Fund criteria, bendamustine may be used in combination with rituximab, which is commissioned by NHS England for this indication[2].

A cohort of patients had been identified through data from individual patient funding request panels and clinicians in Wales considered there to be an unmet need within the service. This cohort includes: young and fit people with aggressive, untreated and relapsed follicular lymphoma and marginal zone lymphoma, and Waldenström's macroglobulinaemia for whom standard therapy is unsuitable. Based on this unmet need, this medicine combination was considered suitable for assessment via the One Wales process.

Current One Wales Interim Commissioning Decision
Bendamustine in combination with rituximab can continue to be made available within NHS Wales for the treatment of previously untreated and relapsed follicular lymphoma, marginal zone lymphoma and Waldenström's macroglobulinaemia under the following circumstances (July 2019):

- In the first-line setting, for use in fit patients with aggressive follicular lymphoma and marginal zone lymphoma where other licensed and health technology appraisal-approved regimens are unsuitable.
- In the relapsed setting, for use in patients with follicular lymphoma and marginal zone lymphoma where other licensed and health technology appraisal-approved regimens are unsuitable.
- For the treatment of Waldenström's macroglobulinaemia for first-line and relapsed disease in patients deemed unsuitable for anthracycline-based regimens and/or where other licensed and health technology appraisal-approved regimens are unsuitable.

Licence status
Bendamustine in combination with rituximab for the treatment of follicular lymphoma, marginal zone lymphoma and Waldenström's macroglobulinaemia remains off-label.

Guidelines
COVID-19: Interim NICE guidance relating to systematic anticancer treatments has been issued to reduce risk to patients and alleviate the impact on service capacity during the COVID-19 pandemic (NG161)[3]. Interim treatment changes are for an initial three-month period. These treatments will be implemented in NHS Wales subject to an interim submission and review process[4]. Treatment regimens will revert to the standard treatment protocol after this period unless the guideline is updated.
Changes recommended in NG161 for Non-Hodgkin's Lymphoma include current suspension of maintenance rituximab and obinutuzumab therapy[5].

In July 2019, the revised European Society for Medical Oncology (ESMO) clinical guidelines for diagnosis, treatment and follow-up of marginal zone lymphomas made recommendations for the use of bendamustine plus rituximab in both extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT lymphoma) and also nodal marginal zone lymphomas with or without monocytoid B cells (NMZL)[6]. Bendamustine plus rituximab was recommended as a treatment option for patients with MALT lymphoma who have symptomatic disseminated disease, contraindications to radiotherapy, treatment failure after antibiotics or after local therapy or suspicion of histological transformation. It was recommended as a treatment option for patients with NMZL[6].

Licensed alternative medicines/Health Technology Appraisal advice for alternative medicines

NICE TA629: Obinutuzumab with bendamustine followed by obinutuzumab maintenance is recommended, within its marketing authorisation, as an option for treating follicular lymphoma that did not respond or progressed up to 6 months after treatment with rituximab or a rituximab-containing regimen. It is recommended only if the company provides it according to the commercial arrangement, May 2020[7].

NICE TA627: Lenalidomide with rituximab is recommended, within its marketing authorisation, as an option for previously treated follicular lymphoma (grade 1 to 3A) in adults. It is only recommended if the company provides lenalidomide according to the commercial arrangement, April 2020[8].

NICE TA604: Idelalisib is not recommended, within its marketing authorisation, for treating refractory follicular lymphoma that has not responded to 2 prior lines of treatment in adults, October 2019[9].

Efficacy/Effectiveness

A repeat literature search conducted by AWTTC identified three retrospective studies.

A published conference abstract, using data from a Medicare database linked to the Surveillance Epidemiology and End Results (SEER) registry, compared the effectiveness of first-line bendamustine plus rituximab with rituximab only in 1,315 older patients (≥ 65 years, median age 78 years) with either NMZL (n = 901) or splenic MZL (SMZL, n = 414)[10]. There was no statistically significant difference in event-free survival (EFS) or overall survival (OS) between the groups. The risk of hospitalisations and transfusions was statistically significantly higher in the bendamustine plus rituximab group[10].

A peer-reviewed study, using the SEER-Medicare database, compared real-life outcomes of older patients with either follicular lymphoma, mantle cell lymphoma or marginal zone/lymphoplasmacytic lymphoma treated with first-line bendamustine plus rituximab or cyclophosphamide-based regimens[11]. Median age of the patients in the analytic cohort (n = 3,491) was 75 years. In the analytic cohort, 1,368 patients who received bendamustine plus rituximab were matched to patients who received RCHOP/RCVP in a 1:1 ratio (n = 2,736). In this cohort, event-free survival (EFS) was statistically significantly better for all patients receiving bendamustine plus rituximab (hazard ratio [HR] 0.78; 95% confidence interval [CI]: 0.70 – 0.87) but there was no such difference for OS (HR 1.03; 95% CI: 0.91 – 1.17). Bendamustine plus rituximab was associated with statistically significantly fewer hospitalisations, infections, transfusions and cardiovascular events than RCHOP/RCVP. In histology-specific subcohorts separately matched in a 1:1 ratio, mantle cell lymphoma patients (n = 690) benefited most from bendamustine plus rituximab treatment in relation to EFS (HR 0.64; 95% CI: 0.54 – 0.76), with less benefit observed for follicular lymphoma patients (n = 1,330; HR 0.83; 95% CI: 0.69 – 0.98) and no significant benefit seen for marginal zone/lymphoplasmacytic lymphoma patients (n = 574; HR 0.92; 95% CI: 0.73 – 1.17)[11].

A second peer-reviewed, retrospective study explored the incidence of progression within 24 months of diagnosis or treatment initiation (POD24) and histological transformation in patients with advanced-stage follicular lymphoma treated with first-line bendamustine plus rituximab and maintenance rituximab (n = 296) by comparing outcomes with a historical cohort treated with RCVP and maintenance rituximab (n = 347)[12]. Median age of the patients receiving bendamustine plus rituximab was 61 years; the characteristics of both groups were mostly similar. When compared with RCVP, bendamustine plus rituximab treatment statistically significantly improved EFS (two-year EFS, 85% versus 76%, p = 0.001) and decreased the incidence of POD24 (13% versus 23%, p = 0.001). There was no statistically significant difference in OS between the groups. A higher proportion of patients receiving bendamustine plus rituximab treatment had evidence of histological transformation when compared with RCVP treatment (76% versus 40%)[12].

Safety
No new safety issues were identified.

Cost effectiveness
No relevant cost-effectiveness analyses were identified in the repeat literature search.

Budget impact
No information on patient numbers has been received.

Impact on health and social care services
The impact on the service remains minimal.

Patient outcome data
No patient outcome data have been provided.

References

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